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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/716,005	Applicant(s) UHL ET AL.	
	Examiner Jehanne S. Sitton	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *23-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22 and 28-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-36* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/04, 3/04, 5/04,* .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: 1449: 6/7/04, 6/17/04, 7/04, 10/04, 4/05.

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1-22 and 28-36, drawn to methods of detecting GBS, classified in class 435, subclass 6.

   II. Claims 23-27, drawn to nucleic acids for detecting GBS, classified in class 536, subclass 23.1.

The inventions are distinct, each from the other because of the following reasons:

2. Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the nucleic acids can be used to encode proteins while the methods can be carried out using immunoassays or culture assays. A search burden exists for searching each of the patentably distinct groups as art relating to the structural requirements of the nucleic acids would not necessarily provide any information regarding bacteria detection and vice versa.

3. Because these inventions are independent or distinct for the reasons given above and have acquired a separate status in the art in view of their different classification, restriction for examination purposes as indicated is proper.

4. Because these inventions are independent or distinct for the reasons given above and the inventions require a different field of search (see MPEP § 808.02), restriction for examination purposes as indicated is proper.

5. During a telephone conversation with Angela Parsons on January 18, 2006 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-22 and 28-36. Affirmation of this election must be made by applicant in replying to this Office action. Claims 23-27 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification

7. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 35 contains the trademark/trade name SYBRGreen1 and SYBRGold. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a double stranded nucleic acid binding dye and, accordingly, the identification/description is indefinite. See MPEP 2173.05(u).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1, 4-9, 11-13, 20-22 and 34-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Telford (Telford et al; WO 02/34771; May 2002) in view of Bellin (Bellin et al; Journal of Clinical Microbiology, January 2001, vol. 39, pages 370-374).

Telford teaches that GBS is known to cause serious neonatal infections. Telford teaches nucleic acids from streptococcus group B (GBS) specifically *S. agalactiae*, including SEQ ID NO: 4465 which is the nucleic acid sequence encoding phosphoenolpyruvate phosphotransferase (ptsI). The specification does not define or provide any guidance as to the limitations of "pts", therefore the term has been given it's broadest reasonable interpretation to encompass ptsI. Telford teaches to make primers and probes using nucleic acids of GBS (see claims 12 and 19-20 of Telford) to detect Streptococcus in a biological sample (see claims 23 and 24 of Telford, also page 6, lines 8-16). Telford does not teach the detection of GBS in a biological sample using LightCycler™ PCR. However, Bellin teaches a method of successfully detecting E. coli in a biological sample using LightCycler™ PCR. With regard to claim 1, Bellin teaches a method for the multiplex real time (claim 11) PCR detection of Enterohemorrhagic (EHEC) E. coli using a primer pair and two fluorescent hybridization probes to detect the stx1 and stx2 genes (see Table 3). Bellin teaches constructing primers and probes from a known sequence and that FRET hybridization probes were marked with LightCycler™ Red 705 and LightCycler™ Red 640 as acceptor dyes (see page 370, col. 2 "PCR primers and Probes; instant claim 7) and fluorescein as the donor (table 3, instant claim 6). The method of Bellin involves continuously

monitoring fluorescence and PCR amplification step (45 cycles; instant claim 13), wherein the biological sample is excited at a wavelength absorbed by a donor fluorescent moiety and measuring the wavelength emitted by the acceptor fluorescent moiety (see page 370, para bridging cols 1 and 2; instant claim 8) thereby quantitating the FRET (instant claim 9). Bellin further teaches determining the melting temperature (claim 12) between the stx1 and stx 2 probes wherein the melting temperature confirms the presence or absence of the Shiga toxin or Shiga toxin like producing organism (see figs 1 and 2). Bellin teaches probes which hybridize within no more than 1 nucleotide (instant claims 4 and 5) of each other (table 3), wherein one probe is labeled with a donor fluorescent moiety and the other probe is labeled with an acceptor fluorescent moiety.

Telford does not teach using a real time single PCR assay using SYBR Green I, however, with regard to claims 34-35, Bellin also teaches a real time single PCR assay for detecting EHEC using a primer pair to detect stx1 and stx2 wherein the amplification product is contacted with SYBR Green I, a double stranded nucleic acid binding dye (see page 370, col. 1, last para; and page 372, col. 1 "PCR optimization and sensitivity").

Bellin teaches that the methods allows for rapid identification of bacteria and complete analysis of up to 32 samples in only 45 minutes.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at time the invention was made to detect GBS using primers and probes to detect ptsI nucleic acids in a biological sample because Telford teaches that GBS causes serious neonatal infections and teaches to use nucleic acids from GBS, including ptsI to detect bacteria in a sample. It would have further been prima facie obvious to the ordinary artisan at the time the invention was made

to modify the identification method of Telford to include construction of primers and probes and the FRET detection methods as taught by Bellin (claims 1, 4-9, 11-13, 20-22) or primers and detection of double stranded DNA using a double stranded DNA binding dye as taught by Bellin (claims 34 and 35) for the purpose of providing a rapid method of detecting GBS in a biological sample. The ordinary artisan would have been motivated to modify the method of Telford with the detection methods of Bellin because Bellin teaches that the use of LightCycler™ PCR allows for rapid identification of bacteria and complete analysis of up to 32 samples in only 45 minutes.

With regard to claims 20-21, Bellin teaches that the cycling step was performed on an EHEC strain (EDL933) already known from a previous study (control sample) to carry stx1 and stx2. With regard to claim 22, Bellin teaches multiplexing stx1 primers and stx2 probes and stx2 primers and stx2 probes were multiplexed in the same assay (see page 372, col. 1), and that the stx double producer EDL933 showed amplification product corresponding to stx1 and stx2 (control amplification product). Therefore, it would have further been prima facie obvious to one of ordinary skill in the art at the time the invention was made to include control sequences, including ptsI sequences from other strains of *S.agalactiae*, as well as other non ptsI nucleic acids to confirm that the primers and probes correctly identified GBS in a sample.

13. Claims 2-3, 10, and 14-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Telford in view of Bellin as applied to claims 1-9, and 11-13 above, and further in view of Wittwer I (Wittwer et al; US Patent 6,140,054, 10/2000).

The method of Telford in view of Bellin is set forth above.

Telford and Bellin do not specifically teach the method wherein the detecting step is performed after each cycling step or wherein the presence of FRET with in 40 or 30 cycles is indicative of GBS. However Wittwer I teaches a general method for detecting targets using primer pairs and adjacent FRET probes, wherein the detecting step is performed after each cycling step (see col 6, lines 33-35, col 16, lines 7-10; instant claim 11). Further, Wittwer I teaches target detection after 30 and 26 cycles (col. 19 lines 14-16 and col. 20, lines 30-35; instant claims 15-16). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of Telford and Bellin by detecting FRET after each cycling step for the purpose of detecting GBS as rapidly as possible. The ordinary artisan would have been motivated to improve the method of Telford and Bellin because Wittwer I teaches the successful identification of targets in as few as 30 and 26 cycles.

Telford and Bellin do not teach primers and probes *comprising* SEQ ID NOS 1-4, however, in performing the method of Telford in view of Bellin, the ordinary artisan would be motivated to construct primers and probes as taught by Bellin for detection of GBS sequences as taught by Telford. Instantly claimed SEQ ID NOS 1-4 are found within SEQ ID NO: 4465 of Telford as follows: SEQ ID NO: 1 is identical to positions 177-199 of SEQ ID NO: 4465, SEQ ID NO: 2 is the reverse complement of positions 357-377 of SEQ ID NO: 4465, SEQ ID NO: 3 is identical to positions 265-289 of SEQ ID NO: 4465, and SEQ ID NO: 4 is identical to positions 292-311 of SEQ ID NO: 4465. Designing primers and probes to known sequences taught in the art is routine experimentation. The prior art teaches the parameters and objectives involved in the selection of oligonucleotides that function as probes and primers, see Wittwer. Moreover there are many internet web sites that provide free downloadable software to aid in the

selection of primers drawn from genetic data recorded in a spreadsheet. The prior art is replete with guidance and information necessary to permit the ordinary artisan in the field of nucleic acid detection to design primers and probes. As discussed above, the ordinary artisan would be motivated to have designed and tested primers and probes that function to detect GBS as taught by Telford, including the instantly claimed nucleic acid sequences comprising SEQ ID NOS 1-4. These sequences are obvious over the teachings of Telford and Bellin and in view of Wittwer. It is noted that an assay using a primer pair consisting of SEQ ID NOS 1-2, with probes consisting of SEQ ID NOS 3 and 4, respectively, did not cross react with other non GBS bacteria, which is unexpected over the teaches of Telford and Bellin in view of Wittwer. The claims, however, are not limited to these SEQ ID NOS due to the recitation of "comprising".

14. Claims 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Telford in view of Bellin as applied to claims 1-9, and 11-13 above, and further in view of Hartley (US Patent 5,035,996; 7/30/1991).

The teachings of Telford in view of Bellin are set forth above.

Telford and Bellin do not teach the method comprising preventing amplification of a contaminant nucleic acid by performing amplification in the presence of uracil and treating the sample with uracil-DNA glycosylase prior to amplification, however Hartley teaches preventing amplification of contaminants by treating samples with uracil DNA glycosylase prior to amplification, and also performing amplification in the presence of uracil. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of Telford and Bellin by preventing amplification of contaminating

nucleic acids with the method of preventing amplification of contaminants taught by Hartley for the purpose of making the method of Telford and Bellin more accurate.

15. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Telford in view of Bellin as applied to claims 1-9 and 11-13 above, and further in view of Bergeron (Bergeron et al; New England Journal of Medicine, 2000, vol. 343, pages 175-179).

The teachings of Telford in view of Bellin are set forth above.

Telford and Bellin do not teach a method of nucleic acid based GBS identification in a biological sample wherein the sample is an anal/and or vaginal swab. However, Bergeron teaches studying the efficacy of PCR assays for routine screening of pregnant women for GBS at the time of delivery. Bergeron teaches obtaining anal, vaginal, and combined anal/vaginal specimens and successfully detecting GBS (see abstract). Bergeron teaches that the sensitivity of the PCR results was 97%. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of PCR based detection of GBS of Telford and Bellin, to include anal and/or vaginal sample specimens as taught by Bergeron. The ordinary artisan would have been motivated to use anal and/or vaginal specimens because Bergeron teaches that such specimens allow for the sensitivity detection of GBS in pregnant women at the time of delivery with a negative predictive value of 98.8%.

16. Claim 36 is rejected under 35 USC 103(a) as being unpatentable over Telford and Bellin as applied to claims 34 and 35 above, in view of Wittwer II (Wittwer et al; US Patent 6,174,670; 1/16/2001).

The teachings of Telford and Bellin are set forth above.

Telford and Bellin do not teach determining the melting temperature between the amplification product and the double stranded nucleic acid binding dye, however Wittwer II teaches determining the melting temperature between the amplification product and double stranded binding dye for the purpose of correcting for nonspecific amplification, improving sensitivity of PCR, monitoring product hybridization, and product quantification by reannealing kinetics (col. 3, lines 30-50). Wittwer II specifically teaches a method of real time monitoring of a PCR reaction by amplifying the target by PCR in the presence of SYBR Green I, exciting the biological sample with light and detecting the emission, and monitoring the temperature dependent fluorescence from SYBR Green I (see col. 7, lines 13-31). Further, Wittwer II specifically teaches analysis using the DNA binding dye ethidium bromide (see col. 11, lines 10-38; col. 22,lines 54-66). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of detection of GBS of Telford and Bellin to include the step of determining the melting temperature between the amplification product and double stranded binding dye, for the purpose of correcting for nonspecific amplification, improving sensitivity of PCR, monitoring product hybridization, and product quantification by reannealing kinetics, as taught by Wittwer II.

17. Claims 28, 32, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Telford in view of Belanger (Belanger et al; Journal of Clinical Microbiology, vol. 40, pages 1436-1440, April 2002) as evidenced by mcrc.com.

The following is evidence of the art accepted structure and function attributed to "molecular beacon probes". Mcrc.com defines molecular beacon probes as: "DNA oligonucleotides that become fluorescent when they hybridize to their target. They are hairpin-shaped, single-stranded molecules consisting of a probe sequence embedded between complementary sequences that form a hairpin stem. A fluorophore is covalently attached to one end of the oligonucleotide and a non-fluorescent quencher is covalently attached to the other end. In the absence of a target, the fluorophore is held close to the quencher and fluorescence cannot occur. When the probe binds to its target, the greater stability of the probe-target helix forces the stem to unwind resulting in a separation of the fluorophore from the quencher, and fluorescence can occur.".

Telford teaches that GBS is known to cause serious neonatal infections. Telford teaches nucleic acids from streptococcus group B (GBS) specifically S. *agalactiae*, including SEQ ID NO: 4465 which is the nucleic acid sequence encoding phosphoenolpyruvate phosphotransferase (ptsI). Telford teaches to make primers and probes using nucleic acids of GBS for (see claims 12 and 19-20 of Telford) to detect Streptococcus in a biological sample (see claims 23 and 24 of Telford, also page 6, lines 8-16). Telford does not teach the detection of GBS in a biological sample using PCR followed by hybridization with a molecular beacon probe labeled with a donor and corresponding acceptor fluorescent moiety.

However, Belanger teaches a method for the detection of shiga toxin producing E. coli by detection of the stx1 and stx2 genes (Shiga like toxin producing organism). The method of Belanger uses a pair of primers to amplify either stx1 or stx2 (amplification step) and a molecular beacon probe (hybridizing step) to detect the presence of the E. coli strains which do

contain the stx1 or stx2 genes and distinguish them from strains that do not (see page 1438, col. 1), using the presence or absence of fluorescence for detection. It is noted that molecular beacon probes comprise a single stranded sequence which permits secondary structure formation (hairpin) wherein the secondary structure results in spatial proximity between the donor and acceptor fluorescent moiety. Further, the acceptor moiety in a molecular beacon probe is a quencher. Belanger teaches that the method is rapid, simple and sensitive and allowed detection of bacteria in a sample where the bacteria were not detected by conventional culture methods (see abstract).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to detect GBS using primers and a probes to detect ptsI nucleic acids in a biological sample because Telford teaches that GBS causes serious neonatal infections and teaches to use nucleic acids from GBS, including ptsI to detect bacteria in a sample. It would have further been prima facie obvious to the ordinary artisan at the time the invention was made to modify the identification method of Telford to include construction of primers and a molecular beacon probe and the fluorescence based PCR methods as taught by Belanger for the purpose of providing a rapid method of detecting GBS in a biological sample. The ordinary artisan would have been motivated to modify the method of Telford with the detection methods of Belanger because Belanger teaches that the use of a molecular beacon probe in a fluorescence based PCR detection method allows for rapid, simple and sensitive identification of bacteria.

18. Claims 28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Telford in view of Pfeffer (Pfeffer et al; WO 98/48046).

Telford teaches that GBS is known to cause serious neonatal infections. Telford teaches nucleic acids from streptococcus group B (GBS) specifically S. *agalactiae*, including SEQ ID NO: 4465 which is the nucleic acid sequence encoding phosphoenolpyruvate phosphotransferase (ptsI). Telford teaches to make primers and probes using nucleic acids of GBS for (see claims 12 and 19-20 of Telford) to detect Streptococcus in a biological sample (see claims 23 and 24 of Telford, also page 6, lines 8-16). Telford does not teach the detection of GBS in a biological sample using a PCR assay that employs the 5'-3' exonuclease activity of Taq polymerase.

However, Pfeffer teaches a method of detecting enterohemorrhagic E. coli by using a PCR assay that employs the 5'-3' exonuclease activity of Taq polymerase (TAQMAN™) together with a flourogenic probe (see page 4, lines 18-23; page 5, lines 24-26; page 9, lines 5-10). Pfeffer teaches that the method utilizes primers (page 8, lines 21-30) and a probe (page 10, lines 15-24) for the detection of the SltI and SltII wherein detection of the presence of fluorescence resonance energy transfer is indicative of the presence of the enterohemorrhagic E. coli (see also, page 25-26 and tables 2- 4). Pfeffer teaches that the use of the TAQMAN™ assay allows for the specific, rapid and high throughput detection of specific bacteria.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to detect GBS using primers and a probes to detect ptsI nucleic acids in a biological sample because Telford teaches that GBS causes serious neonatal infections and teaches to use nucleic acids from GBS, including ptsI to detect bacteria in a sample. It would have further been prima facie obvious to the ordinary artisan at the time the invention was made to modify the identification method of Telford to include construction of primers and a flourescent probe as taught by Pfeffer for the purpose of providing a rapid method of detecting

GBS in a biological sample. The ordinary artisan would have been motivated to modify the method of Telford with the detection methods of Pfeffer because Pfeffer teaches that the use of a fluorescently labeled probe in a TAQMAN™ detection method allows for rapid, simple and sensitive identification of bacteria.

19. Claims 30-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Telford in view of Pfeffer as applied to claims 28 and 29 above, and further in view of Livak et al (US Patent 5,538,848 1995).

The teachings of Telford and Pfeffer are set forth above.

Telford and Pfeffer do not teach a method wherein the donor and acceptor moieties are within no more than 5 nucleotides of each other on the probe, however, Livak teaches a method of detecting hybridization of flourogenic probe in a 5' nucleic assay, and teaches that traditionally, the donor and quencher are separated by about 6-16 nucleotides of each other on the probe (see col. 2, lines 45-50). The recitation of "about 6" has been interpreted to encompass 5 nucleotides apart. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Telford and Pfeffer to use probes wherein the donor and quencher are within no more than 5 nucleotides of each other because Livak teaches that such orientation provides sufficient spacing for the purposes of detecting hybridization of the probe in the 5'nuclease (Taqman) assay. The ordinary artisan would have been motivated to modify the probe used by Telford and Pfeffer as taught by Livak for the purpose of making the method of Telford and Pfeffer more versatile to perform.

20. Claims 1-18, 20-22 and 28-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Telford in view of Uhl (Uhl et al; US patent 6,593,093).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). *This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).*

Telford teaches that GBS is known to cause serious neonatal infections. Telford teaches nucleic acids from streptococcus group B (GBS) specifically *S. agalactiae*, including SEQ ID NO: 4465 which is the nucleic acid sequence encoding phosphoenolpyruvate phosphotransferase (ptsI). Telford teaches to make primers and probes using nucleic acids of GBS (see claims 12 and 19-20 of Telford) to detect Streptococcus in a biological sample (see claims 23 and 24 of Telford, also page 6, lines 8-16). Telford does not teach the detection of GBS in a biological sample using LightCycler™ PCR, molecular beacon probes, or the TAQMAN™ assay.

However, Uhl teaches a method of successfully detecting Group A Streptococcus (GAS) in a biological sample by using primers and probes to pstI nucleic acids using various methods including LightCycler™ PCR, molecular beacon probes, or the TAQMAN™ assay (see claims 1-21 and 27-35 of Uhl). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to detect GBS using primers and a probes to detect ptsI nucleic acids in a biological sample because Telford teaches that GBS causes serious neonatal infections and teaches to use nucleic acids from GBS, including ptsI to detect bacteria in a sample. It would have further been prima facie obvious to the ordinary artisan at the time the invention was made to modify the identification method of Telford to include construction of primers and probes for use in LightCycler™ PCR, molecular beacon probe assays, and the TAQMAN™ assay as taught by Uhl for the purpose of providing a method of detecting GBS in a biological sample. The ordinary artisan would have been motivated to modify the method of Telford with the detection methods of Uhl because Uhl teaches that the use of LightCycler™ PCR, molecular beacon probe assays, and the TAQMAN™ allows for sensitive identification of streptococcus bacteria.

Additionally, instantly claimed SEQ ID NO: 2 is identical to SEQ ID NO: 2 of Uhl. Telford and Uhl do not teach primers and probes *comprising* SEQ ID NOS 1, and 3-4, however, in performing the method of Telford in view of Uhl, the ordinary artisan would be motivated to construct primers and probes as taught by Uhl for detection of GBS sequences as taught by Telford. Instantly claimed SEQ ID NOS 1-4 are found within SEQ ID NO: 4465 of Telford as follows: SEQ ID NO: 1 is identical to positions 177-199 of SEQ ID NO: 4465, SEQ ID NO: 2 is the reverse complement of positions 357-377 of SEQ ID NO: 4465, SEQ ID NO: 3 is identical to

positions 265-289 of SEQ ID NO: 4465, and SEQ ID NO: 4 is identical to positions 292-311 of SEQ ID NO: 4465. Designing primers and probes to known sequences taught in the art is routine experimentation. The prior art teaches the parameters and objectives involved in the selection of oligonucleotides that function as probes and primers, see Uhl. Moreover there are many internet web sites that provide free downloadable software to aid in the selection of primers drawn from genetic data recorded in a spreadsheet. The prior art is replete with guidance and information necessary to permit the ordinary artisan in the field of nucleic acid detection to design primers and probes. As discussed above, the ordinary artisan would be motivated to have designed and tested primers and probes that function to detect GBS as taught by Telford, including the instantly claimed nucleic acid sequences comprising SEQ ID NOS 1-4.

21. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Telford in view of Uhl as applied to claims 1-9 and 11-13 above, and further in view of Bergeron (Bergeron et al; New England Journal of Medicine, 2000, vol. 343, pages 175-179).

The teachings of Telford in view of Uhl are set forth above.

Telford and Uhl do not teach a method of nucleic acid based GBS identification in a biological sample wherein the sample is an anal/and or vaginal swab. However, Bergeron teaches studying the efficacy of PCR assays for routine screening of pregnant women for GBS at the time of delivery. Bergeron teaches obtaining anal, vaginal, and combined anal/vaginal specimens and successfully detecting GBS (see abstract). Bergeron teaches that the sensitivity of the PCR results was 97%. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of PCR based detection

of GBS of Telford and Uhl, to include anal and/or vaginal sample specimens as taught by Bergeron. The ordinary artisan would have been motivated to use anal and/or vaginal specimens because Bergeron teaches that such specimens allow for the sensitivity detection of GBS in pregnant women at the time of delivery with a negative predictive value of 98.8%.

22. Claims 1, 4-9, 11-13, 20-22 and 34-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tettelin (Tettelin et al; PNAS, 9/2002, vol. 99, pages 12391-12396) and Genbank Accession number NC_004368 (November 15, 2002) in view of Bellin (Bellin et al; Journal of Clinical Microbiology, January 2001, vol. 39, pages 370-374).

Tettelin teaches that GBS is known to cause serious neonatal infections. Tettelin teaches nucleic acids from streptococcus group B (GBS) and teaches that while *S. agalactiae*, lacks the systems of other streptococcus (GAS and SP) for metabolism of fucose, lactose, mannitol, raffinose, lysine, and threonine, it has a galactitol PTS. Genbank Accession number NC_004368 teaches the sequence of S. agalactiae, including the galactitol PTS. The specification does not define or provide any guidance as to the limitations of "pts", therefore the term has been given it's broadest reasonable interpretation to encompass galactitol PTS. Tettelin and '004368 do not teach the detection of GBS in a biological sample using LightCycler™ PCR. However, Bellin teaches a method of successfully detecting E. coli in a biological sample using LightCycler™ PCR. With regard to claim 1, Bellin teaches a method for the multiplex real time (claim 11) PCR detection of Enterohemorrhagic (EHEC) E. coli using a primer pair and two fluorescent hybridization probes to detect the stx1 and stx2 genes (see Table 3). Bellin teaches constructing primers and probes from a known sequence and that FRET hybridization probes were marked

with LightCycler™ Red 705 and LightCycler™ Red 640 as acceptor dyes (see page 370, col. 2 "PCR primers and Probes; instant claim 7) and fluorescein as the donor (table 3, instant claim 6). The method of Bellin involves continuously monitoring fluorescence and PCR amplification step (45 cycles; instant claim 13), wherein the biological sample is excited at a wavelength absorbed by a donor fluorescent moiety and measuring the wavelength emitted by the acceptor fluorescent moiety (see page 370, para bridging cols 1 and 2; instant claim 8) thereby quantitating the FRET (instant claim 9). Bellin further teaches determining the melting temperature (claim 12) between the stx1 and stx 2 probes wherein the melting temperature confirms the presence or absence of the Shiga toxin or Shiga toxin like producing organism (see figs 1 and 2). Bellin teaches probes which hybridize within no more than 1 nucleotide (instant claims 4 and 5) of each other (table 3), wherein one probe is labeled with a donor fluorescent moiety and the other probe is labeled with an acceptor fluorescent moiety.

Tettelin and '004368 do not teach using a real time single PCR assay using SYBR Green I, however, with regard to claims 34-35, Bellin also teaches a real time single PCR assay for detecting EHEC using a primer pair to detect stx1 and stx2 wherein the amplification product is contacted with SYBR Green I, a double stranded nucleic acid binding dye (see page 370, col. 1, last para; and page 372, col. 1 "PCR optimization and sensitivity").

Bellin teaches that the methods allows for rapid identification of bacteria and complete analysis of up to 32 samples in only 45 minutes.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at time the invention was made to detect GBS using primers and probes to detect PTS nucleic acids in a biological sample because Tettelin teaches that GBS causes serious neonatal infections and

teaches that galactitol PTS is found in GBS as opposed to other streptococcus bacteria. It would have further been prima facie obvious to the ordinary artisan at the time the invention was made to use the identification method of Bellin to detect GBS using PTS nucleic acids as taught by Tettelin and '004368 and to include construction of primers and probes and the FRET detection methods as taught by Bellin (claims 1, 4-9, 11-13, 20-22) or primers and detection of double stranded DNA using a double stranded DNA binding dye as taught by Bellin (claims 34 and 35) for the purpose of providing a rapid method of detecting GBS in a biological sample. The ordinary artisan would have been motivated to use the nucleic acids of Tettelin and '004368 with the detection methods of Bellin because Bellin teaches that the use of LightCycler™ PCR allows for rapid identification of bacteria and complete analysis of up to 32 samples in only 45 minutes.

With regard to claims 20-21, Bellin teaches that the cycling step was performed on an EHEC strain (EDL933) already known from a previous study (control sample) to carry stx1 and stx2. With regard to claim 22, Bellin teaches multiplexing stx1 primers and stx2 probes and stx2 primers and stx2 probes were multiplexed in the same assay (see page 372, col. 1), and that the stx double producer EDL933 showed amplification product corresponding to stx1 and stx2 (control amplification product). Therefore, it would have further been prima facie obvious to one of ordinary skill in the art at the time the invention was made to include control sequences, including galactitol PTS sequences from other strains of *S.agalactiae*, as well as other non PTS nucleic acids to confirm that the primers and probes correctly identified GBS in a sample.

23. Claims 10, and 14-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tettelin and '004368 in view of Bellin as applied to claims 1-9, and 11-13 above, and further in view of Wittwer I (Wittwer et al; US Patent 6,140,054, 10/2000).

The method of Tettelin and '004368 in view of Bellin is set forth above.

Tettelin and '004368 and Bellin do not specifically teach the method wherein the detecting step is performed after each cycling step or wherein the presence of FRET with in 40 or 30 cycles is indicative of GBS. However Wittwer I teaches a general method for detecting targets using primer pairs and adjacent FRET probes, wherein the detecting step is performed after each cycling step (see col 6, lines 33-35, col 16, lines 7-10; instant claim 11). Further, Wittwer I teaches target detection after 30 and 26 cycles (col. 19 lines 14-16 and col. 20, lines 30-35; instant claims 15-16). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of Tettelin and '004368 in view of Bellin by detecting FRET after each cycling step for the purpose of detecting GBS as rapidly as possible. The ordinary artisan would have been motivated to improve the method of Tettelin and '004368 in view of Bellin because Wittwer I teaches the successful identification of targets in as few as 30 and 26 cycles.

24. Claims 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tettelin and '004368 in view of Bellin as applied to claims 1-9, and 11-13 above, and further in view of Hartley (US Patent 5,035,996; 7/30/1991).

The teachings of Tettelin and '004368 in view of Bellin are set forth above.

Tettelin and '004368 in view of Bellin do not teach the method comprising preventing amplification of a contaminant nucleic acid by performing amplification in the presence of uracil and treating the sample with uracil-DNA glycosylase prior to amplification, however Hartley teaches preventing amplification of contaminants by treating samples with uracil DNA glycosylase prior to amplification, and also performing amplification in the presence of uracil. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of Tettelin and '004368 in view of Bellin by preventing amplification of contaminating nucleic acids with the method of preventing amplification of contaminants taught by Hartley for the purpose of making the method of Tettelin and '004368 in view of Bellin more accurate.

25. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tettelin and '004368 in view of Bellin as applied to claims 1-9 and 11-13 above, and further in view of Bergeron (Bergeron et al; New England Journal of Medicine, 2000, vol. 343, pages 175-179).

The teachings of Tettelin and '004368 in view of Bellin are set forth above.

Tettelin and '004368 in view of Bellin do not teach a method of nucleic acid based GBS identification in a biological sample wherein the sample is an anal/and or vaginal swab. However, Bergeron teaches studying the efficacy of PCR assays for routine screening of pregnant women for GBS at the time of delivery. Bergeron teaches obtaining anal, vaginal, and combined anal/vaginal specimens and successfully detecting GBS (see abstract). Bergeron teaches that the sensitivity of the PCR results was 97%. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the

method of PCR based detection of GBS of Tettelin and '004368 in view of Bellin, to include anal and/or vaginal sample specimens as taught by Bergeron. The ordinary artisan would have been motivated to use anal and/or vaginal specimens because Bergeron teaches that such specimens allow for the sensitivity detection of GBS in pregnant women at the time of delivery with a negative predictive value of 98.8%.

26. Claim 36 is rejected under 35 USC 103(a) as being unpatentable over Tettelin and '004368 in view of Bellin as applied to claims 34 and 35 above, in view of Wittwer II (Wittwer et al; US Patent 6,174,670; 1/16/2001).

The teachings of Tettelin and '004368 in view of Bellin are set forth above.

Tettelin and '004368 in view of Bellin do not teach determining the melting temperature between the amplification product and the double stranded nucleic acid binding dye, however Wittwer II teaches determining the melting temperature between the amplification product and double stranded binding dye for the purpose of correcting for nonspecific amplification, improving sensitivity of PCR, monitoring product hybridization, and product quantification by reannealing kinetics (col. 3, lines 30-50). Wittwer II specifically teaches a method of real time monitoring of a PCR reaction by amplifying the target by PCR in the presence of SYBR Green I, exciting the biological sample with light and detecting the emission, and monitoring the temperature dependent fluorescence from SYBR Green I (see col. 7, lines 13-31). Further, Wittwer II specifically teaches analysis using the DNA binding dye ethidium bromide (see col. 11, lines 10-38; col. 22,lines 54-66). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of detection

of GBS of Tettelin and '004368 in view of Bellin to include the step of determining the melting temperature between the amplification product and double stranded binding dye, for the purpose of correcting for nonspecific amplification, improving sensitivity of PCR, monitoring product hybridization, and product quantification by reannealing kinetics, as taught by Wittwer II.

27. Claims 28, 32, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tettelin and '004368 in view of Belanger (Belanger et al; Journal of Clinical Microbiology, vol. 40, pages 1436-1440, April 2002) as evidenced by mcrc.com.

The following is evidence of the art accepted structure and function attributed to "molecular beacon probes". Mcrc.com defines molecular beacon probes as: "DNA oligonucleotides that become fluorescent when they hybridize to their target. They are hairpin-shaped, single-stranded molecules consisting of a probe sequence embedded between complementary sequences that form a hairpin stem. A fluorophore is covalently attached to one end of the oligonucleotide and a non-fluorescent quencher is covalently attached to the other end. In the absence of a target, the fluorophore is held close to the quencher and fluorescence cannot occur. When the probe binds to its target, the greater stability of the probe-target helix forces the stem to unwind resulting in a separation of the fluorophore from the quencher, and fluorescence can occur.".

Tettelin teaches that GBS is known to cause serious neonatal infections. Tettelin teaches nucleic acids from streptococcus group B (GBS) and teaches that while *S. agalactiae*, lacks the systems of other streptococcus (GAS and SP) for metabolism of fucose, lactose, mannitol, raffinose, lysine, and threonine, it has a galactitol PTS. Genbank Accession number NC_004368

teaches the sequence of S. agalactiae, including the galactitol PTS. The specification does not define or provide any guidance as to the limitations of "pts", therefore the term has been given it's broadest reasonable interpretation to encompass galactitol PTS. Tettelin and '004368 do not teach the detection of GBS in a biological sample using PCR followed by hybridization with a molecular beacon probe labeled with a donor and corresponding acceptor fluorescent moiety.

However, Belanger teaches a method for the detection of shiga toxin producing E. coli by detection of the stx1 and stx2 genes. The method of Belanger uses a pair of primers to amplify either stx1 or stx2 (amplification step) and a molecular beacon probe (hybridizing step) to detect the presence of the E. coli strains which do contain the stx1 or stx2 genes and distinguish them from strains that do not (see page 1438, col. 1), using the presence or absence of fluorescence for detection. It is noted that molecular beacon probes comprise a single stranded sequence which permits secondary structure formation (hairpin) wherein the secondary structure results in spatial proximity between the donor and acceptor fluorescent moiety. Further, the acceptor moiety in a molecular beacon probe is a quencher. Belanger teaches that the method is rapid, simple and sensitive and allowed detection of bacteria in a sample where the bacteria were not detected by conventional culture methods (see abstract).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at time the invention was made to detect GBS using primers and probes to detect PTS nucleic acids in a biological sample because Tettelin teaches that GBS causes serious neonatal infections and teaches that galactitol PTS is found in GBS as opposed to other streptococcus bacteria. It would have further been prima facie obvious to the ordinary artisan at the time the invention was made to use the identification method of Belanger to detect GBS using PTS nucleic acids as taught by

Tettelin and '004368 and to include construction of primers and molecular beacon probes and the and the fluorescence based PCR methods as taught by Belanger for the purpose of providing a rapid method of detecting GBS in a biological sample. The ordinary artisan would have been motivated to use the nucleic acids of Tettelin and '004368 with the detection methods of Belanger because Belanger teaches that the use of a molecular beacon probe in a fluorescence based PCR detection method allows for rapid, simple and sensitive identification of bacteria.

28. Claims 28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tettelin and '004368 in view of Pfeffer (Pfeffer et al; WO 98/48046).

Tettelin teaches that GBS is known to cause serious neonatal infections. Tettelin teaches nucleic acids from streptococcus group B (GBS) and teaches that while *S. agalactiae*, lacks the systems of other streptococcus (GAS and SP) for metabolism of fucose, lactose, mannitol, raffinose, lysine, and threonine, it has a galactitol PTS. Genbank Accession number NC_004368 teaches the sequence of *S. agalactiae*, including the galactitol PTS. The specification does not define or provide any guidance as to the limitations of "pts", therefore the term has been given it's broadest reasonable interpretation to encompass galactitol PTS. Tettelin and '004368 do not teach the detection of GBS in a biological sample using a PCR assay that employs the 5'-3' exonuclease activity of Taq polymerase.

However, Pfeffer teaches a method of detecting enterohemorrhagic E. coli by using a PCR assay that employs the 5'-3' exonuclease activity of Taq polymerase (TAQMAN™) together with a flourogenic probe (see page 4, lines 18-23; page 5, lines 24-26; page 9, lines 5-10). Pfeffer teaches that the method utilizes primers (page 8, lines 21-30) and a probe (page 10,

lines 15-24) for the detection of the SltI and SltII wherein detection of the presence of fluorescence resonance energy transfer is indicative of the presence of the enterohemorrhagic E. coli (see also, page 25-26 and tables 2- 4). Pfeffer teaches that the use of the TAQMAN™ assay allows for the specific, rapid and high throughput detection of specific bacteria.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at time the invention was made to detect GBS using primers and probes to detect PTS nucleic acids in a biological sample because Tettelin teaches that GBS causes serious neonatal infections and teaches that galactitol PTS is found in GBS as opposed to other streptococcus bacteria. It would have further been prima facie obvious to the ordinary artisan at the time the invention was made to use the identification method of Belanger to detect GBS using PTS nucleic acids as taught by Tettelin and '004368 and to include construction of primers and a flourescent probe as taught by Pfeffer for the purpose of providing a rapid method of detecting GBS in a biological sample. The ordinary artisan would have been motivated to use the nucleic acids of Tettelin and '004368 with the detection methods of Pfeffer because Pfeffer teaches that the use of a fluorescently labeled probe in a TAQMAN™ detection method allows for rapid, simple and sensitive identification of bacteria.

29. Claims 30-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tettelin and '004368 in view of Pfeffer as applied to claims 28 and 29 above, and further in view of Livak et al (US Patent 5,538,848 1995).

The teachings of Tettelin and '004368 in view of Pfeffer are set forth above.

Tettelin and '004368 in view of Pfeffer do not teach a method wherein the donor and acceptor moieties are within no more than 5 nucleotides of each other on the probe, however, Livak teaches a method of detecting hybridization of flourogenic probe in a 5' nucleic assay, and teaches that traditionally, the donor and quencher are separated by about 6-16 nucleotides of each other on the probe (see col. 2, lines 45-50). The recitation of "about 6" has been interpreted to encompass 5 nucleotides apart. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Tettelin and '004368 in view of Pfeffer to use probes wherein the donor and quencher are within no more than 5 nucleotides of each other because Livak teaches that such orientation provides sufficient spacing for the purposes of detecting hybridization of the probe in the 5'nuclease (Taqman) assay. The ordinary artisan would have been motivated to modify the probe used by Tettelin and '004368 in view of Pfeffer as taught by Livak for the purpose of making the method of Tettelin and '004368 in view of Pfeffer more versatile to perform.

Conclusion

30. No claims are allowed.

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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6/20/06